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WO 03/002543 A1

(54) Title: PYRIMIDINOXYALKYLPIPERAZINES AND THEIR THERAPEUTIC USE

(57) Abstract: Pyrimidinoxyalkylpiperazines of the formula (I) in which n represents an integer from 2 to 6, R_1 represents H, C_1-C_6-alkyl or phenyl (C_1-C_6)-alkyl in which the phenyl radical can be substituted by one or more substituents selected from C_1-C_6-alkyl and C_1-C_6-alkoxy, R_2 represents H, C_1-C_4-alkyl, OH, C_1-C_6-alkoxy, NH_2 or C_1-C_6-halogenoalkyl, R_3 and R_4, independently of each other, represent H, C_1-C_6-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-halogenoalkyl, pyrrolyl or phenyl, which latter can be substituted by one or more substituents selected from C_1-C_6-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxy, OH, halogen or C_1-C_6-halogenoalkyl, phenyl, cyano or nitro. The compounds can be used for treating diseases which respond to modulation of the dopamine D_3 receptor and are characterized by a high degree of bioavailability.

Pyrimidinoxyalkylpiperazines and their therapeutic use

Description

The present invention relates to pyrimidinoxyalkylpiperazines and their therapeutic use. The compounds possess valuable therapeutic properties and can be used, in particular for treating diseases which respond to modulation of the dopamine D_3 receptor.

Neurones obtain their information by way of G protein-coupled receptors, inter alia. There are a large number of substances which exert their effect by way of these receptors. One of these substances is dopamine.

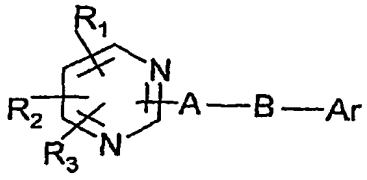
Firm insights exist with regard to the presence of dopamine and its physiological function as a neurotransmitter. Disturbances in the dopaminergic transmitter system result in diseases of the central nervous system which include, for example, schizophrenia, depression and Parkinson's disease. These and other diseases are treated with drugs which interact with the dopamine receptors.

Up until 1990, two subtypes of dopamine receptor had been clearly defined pharmacologically, namely the D_1 and D_2 receptors. More recently, a third subtype has been found, namely the D_3 receptor, which appears to be able to mediate some effects of the antipsychotic agents and anti-Parkinson agents (J.C. Schwartz et al., The Dopamine D_3 Receptor as a Target for Antipsychotics, in Novel Antipsychotic Drugs, H.Y. Meltzer, Ed. Raven Press, New York 1992, pages 135-144; M. Dooley et al., Drugs and Aging 1998, 12, 495-514).

Since D_3 receptors are principally expressed in the limbic system, it is assumed that, while a selective D_3 ligand should probably have the properties of known antipsychotic agents, it should not have their dopamine

D_2 receptor-mediated neurological secondary effects (P. Sokoloff et al., Localization and Function of the D_3 Dopamine Receptor, Arzneim. Forsch./Drug Res. 42(1), 224 (1992); P. Sokoloff et al., Molecular Cloning and Characterization of a Novel Dopamine Receptor (D_3) as a Target for Neuroleptics, Nature, 347, 146 (1990)).

WO 96/02519 discloses substituted pyrimidine compounds of the Formula

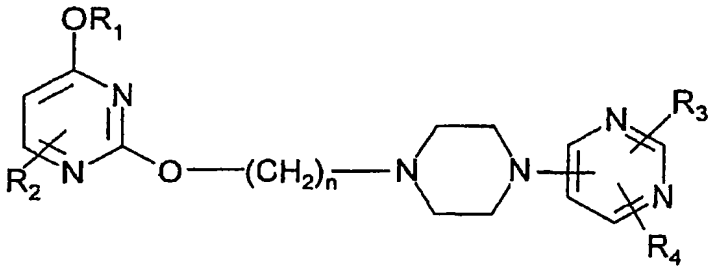


in which R_1, R_2, R_3, A, B and Ar have defined meanings. The compounds of WO 96/02519 are selective dopamine D_3 receptor ligands and are effective, inter alia, for treating schizophrenia, depression and psychoses.

It is desirable to have available selective dopamine D_3 receptor ligands which exhibit a high degree of bioavailability, in particular a high degree of cerebral availability. Compounds which exhibit a high degree of bioavailability have the advantage that a given threshold concentration of the drug at the site of action can be achieved using a lower dose which is to be administered orally. Conversely, when a given dose is administered, a higher concentration of the drug is achieved at the site of action.

The invention is therefore based on the object of making available selective dopamine D_3 receptor ligands which exhibit a high degree of bioavailability.

This object is achieved by means of pyrimidinoxyalkyl-piperazines of the Formula I



I

in which

n represents an integer from 2 to 6,

R_1 represents H, C_1-C_6-alkyl or phenyl-(C_1-C_6)-alkyl in which the phenyl radical can be substituted by one or more substituents selected from C_1-C_6-alkyl and C_1-C_6-alkoxy,

R_2 represents H, C_1-C_4-alkyl, OH, C_1-C_6-alkoxy, NH_2 or C_1-C_6-halogenoalkyl,

R_3 and R_4, independently of each other, represent H, C_1-C_6-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-halogenoalkyl, pyrrolyl or phenyl, which latter can be substituted by one or more substituents selected from C_1-C_6-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxy, OH, halogen or C_1-C_6-halogenoalkyl, phenyl, cyano or nitro,

with the proviso that the radicals R_3 and R_4 on the pyrimidine ring are in each case arranged in the m position (metaposition) in relation to each other and to the piperazine substituent on the pyrimidine ring, and at least one of the radicals R_3 and R_4 represents C_3-C_6-alkyl or C_3-C_6-hydroxyalkyl, which in each case possesses a branched alkyl chain or is bonded to the pyrimidine ring by way of a secondary carbon atom, or trifluoromethyl,

and their piperazine-N-oxides and salts with pharmaceutically tolerated acids.

Within the context of the present application:

Halogen denotes: fluorine, chlorine, bromine or iodine;

C_1-C_6-alkyl denotes: methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-3-methylpropyl;

C_1-C_6-alkoxy denotes; C_1-C_6-alkyloxy containing a C_1-C_6-alkyl radical as mentioned above;

C_1-C_6-halogenoalkyl denotes: a C_1-C_6-alkyl radical, as mentioned above, in which one or more hydrogen atoms is/are substituted by fluorine, chlorine, bromine and/or iodine;

C_1-C_6-hydroxyalkyl denotes: a C_1-C_6-alkyl radical, as mentioned above, in which one or more hydrogen atoms is/are replaced with hydroxyl groups;

C_3-C_6-alkyl or C_3-C_6-hydroxyalkyl, which is bonded by way of a secondary or tertiary carbon atom, denotes: a (hydroxy)alkyl radical having from 3 to 6 carbon atoms in which the carbon atom, by way of which the (hydroxy)alkyl radical is linked to the basic molecule, is linked to 2 or 3 further carbon atoms in the (hydroxy)alkyl radical; such as 1-methylethyl, 1-methylpropyl, 1,1-dimethylethyl, 1-methylbutyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1-methylpentyl, 1,1-dimethylbutyl, 1-ethylbutyl, 1,1,2-trimethylpropyl, 1-

ethyl-1-methylpropyl and 1-ethyl-3-methylpropyl; or the said radicals in which one or more hydrogen atoms is/are replaced with hydroxyl groups.

In the pyrimidinoxyalkylpiperazines of the Formula I, at least one of the radicals R_3 and R_4 preferably represents C_3-C_6-alkyl which is bonded to the pyrimidine ring by way of a secondary or tertiary carbon atom, preferably 1-methylethyl or 1,1-dimethylethyl, or C_3-C_6-hydroxyalkyl which is bonded to the pyrimidine ring by way of a secondary or tertiary carbon atom, preferably 2-hydroxy-1-methylethyl or 2-hydroxy-1,1-dimethylethyl.

In the pyrimidinoxyalkylpiperazines of the Formula I, R_1 preferably represents H or benzyl whose phenyl radical can be substituted by one or more, preferably 1, 2 or 3, C_1-C_6-alkoxy radicals, for example 3,4-dimethyloxybenzyl, 4-methoxybenzyl, 2,3,4-trimethoxybenzyl, 3,4,5-trimethoxybenzyl or 2,5-dimethoxybenzyl.

In the pyrimidinoxyalkylpiperazines of the Formula I, R_1 represents, in particular, H.

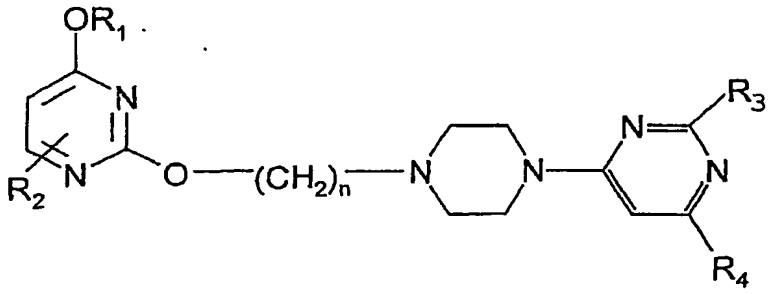
In the pyrimidinoxyalkylpiperazines of the Formula I, R_2 preferably represents H, methyl, ethyl, OH, C_1-C_6-alkoxy, trifluoromethyl or difluoromethyl; and in particular represents H or OH.

In the pyrimidinoxyalkylpiperazines of the Formula I, R_3 and R_4 preferably represent, independently of each other, H, C_1-C_6-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-halogenoalkyl or phenyl, which latter can be substituted by one or more substituents selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen or phenyl.

In the pyrimidinoxyalkylpiperazines of the Formula I, n preferably represents 3 or 4.

Preferred embodiments of the pyrimidinoxyalkyl-

piperazines according to the invention are those of the Formula Ia



Ia

in which R_1, R_2, R_3, R_4 and n have the abovementioned meanings and preferred meanings.

More strongly preferred embodiments of the pyrimidinoxyalkylpiperazines of the Formula Ia are those in which R_3 represents C_3-C_6-alkyl which is bonded to the pyrimidine ring by way of a tertiary carbon atom, and

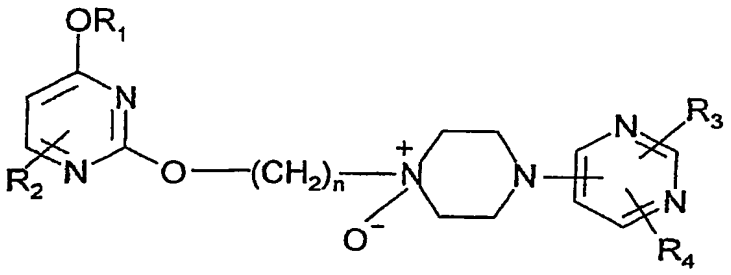
R_4 represents C_1-C_6-alkyl, C_1-C_6-halogenoalkyl or phenyl, which latter can be substituted by one or more substituents selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen or phenyl.

Other preferred embodiments of the pyrimidinoxyalkyl-piperazines of the Formula Ia are those in which R_3 represents trifluoromethyl and R_4 represents C_1-C_6-alkyl, C_1-C_6-halogenoalkyl or phenyl.

The invention also encompasses the acid addition salts of the pyrimidinoxyalkylpiperazines of the Formula I with physiologically tolerated acids. Examples of suitable physiologically tolerated organic and inorganic acids are hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, oxalic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, adipic acid and benzoic acid. Other acids which can be used are described in Fortschritte der Arzneimittel-

forschung [Advances in Drug Research], Volume 10, p. 224 ff., Birkhäuser-Verlag, Basel and Stuttgart, 1966.

The invention also relates to the piperazine-N-oxides of compounds of the Formula I which can be depicted by the following formula

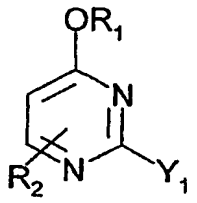


They are obtained by treating a compound of the Formula I with an oxidizing agent, in particular an inorganic or organic peroxide or hydroperoxide, such as hydrogen peroxide, or percarboxylic acids, such as peracetic acid, perbenzoic acid or m-chloroperbenzoic acid.

The pyrimidinoxyalkylpiperazines of the Formula I can be prepared in a variety of ways. They are preferably obtained using one of the following processes A or B.

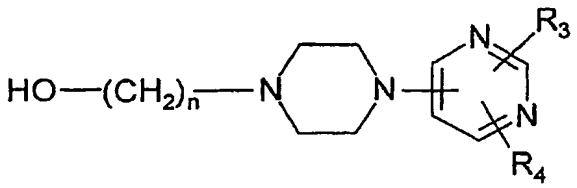
Process A

The compounds according to the invention can be obtained by reacting a compound of the Formula II



II

with a compound of the Formula III



III

in which Y_1 represents a leaving group which can be displaced nucleophilically, such as halogen, C_1-C_6-alkylthio, C_1-C_6-alkylsulphonyl, C_1-C_6-alkylsulphinyl or the like, and R_1, R_2, R_3, R_4 and n have the meaning which have already been indicated.

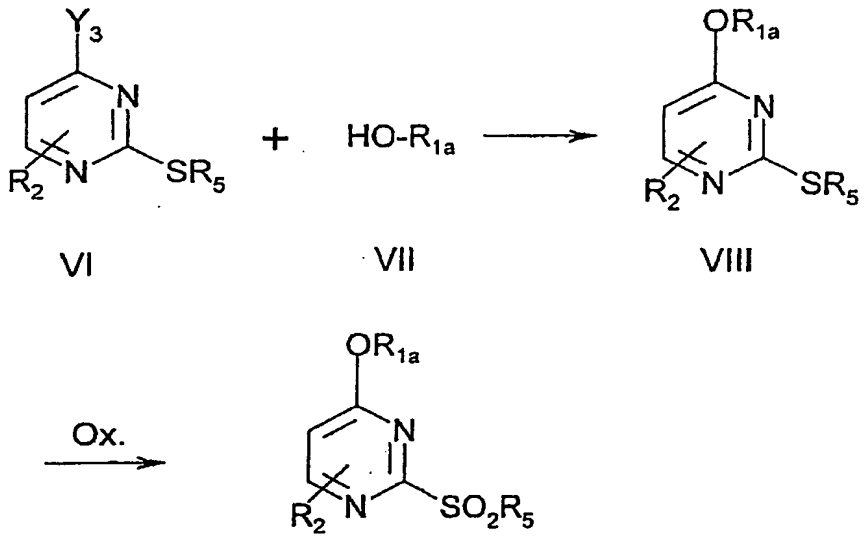
The reaction is preferably carried out in the presence of a diluent. All the solvents which are inert towards the reagents employed can be used for this purpose. Examples of these diluents are water and aliphatic, alicyclic and aromatic hydrocarbons which can in each case be chlorinated, where appropriate, such as hexane, cyclohexane, petroleum ether, ligroin, benzene, toluene, xylene, methylene chloride, chloroform, carbon tetrachloride, ethyl chloride and trichloroethylene, ethers, such as diisopropyl ether, dibutyl ether, methyl tert-butyl ether, dioxane and tetrahydrofuran, ketones, such as acetone, methyl ethyl ketone, methyl isopropyl ketone and methyl isobutyl ketone, nitriles, such as acetonitrile and propionitrile, alcohols, such as methanol, ethanol, isopropanol, butanol and ethylene glycol, esters, such as ethyl acetate and amyl acetate, acid amides, such as dimethylformamide, dimethyl-acetamide and N-methylpyrrolidone, sulphoxides and sulphones, such as dimethyl sulphoxide and sulpholane, bases, such as pyridine, and cyclic ureas, such as 1,3-dimethylimidazolidin-2-one and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone.

In this connection, the reaction is preferably carried out in a temperature range of between 0°C and the boiling point of the diluent. The reaction preferably takes place in the added presence of a suitable base.

An alkali metal or alkaline earth metal hydride, such as sodium hydride, potassium hydride or calcium hydride, a carbonate, such as alkali metal carbonate, e.g. sodium carbonate or potassium carbonate, an alkali metal hydroxide or alkaline earth metal hydroxide, such as sodium hydroxide or potassium hydroxide, an organometallic compound, such as butyllithium, or an alkali metal amide, such as lithium diisopropylamide, can serve as the base.

The compounds of the Formula II are known or can be prepared in a customary manner.

Compounds of the Formula II, in which Y_1 represents C_1-C_6-alkylsulphonyl, can be obtained, for example, by means of a two-step reaction, with a mercaptopyrimidine of the Formula VI, in which Y_3 represents halogen, in particular chlorine, bromine or iodine, and R_5 represents C_1-C_6-alkyl, initially being reacted with an alcohol of the Formula VII, in which R_{1a} has the meanings given for R_1 with the exception of H, and the resulting intermediate of the Formula VIII being oxidized with an oxidizing agent for oxidizing the C_1-C_6-alkylthio group to the C_1-C_6-alkylsulphonyl group.



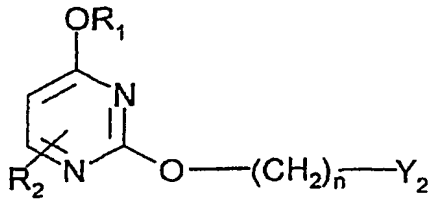
Examples of suitable oxidizing agents are halogens, such as chlorine or bromine, peroxides or peracids, such as hydrogen peroxide or perbenzoic acid, perhalogenates, such as sodium periodate, transition metal oxidizing agents, such as disodium tungstate or potassium permanganate, and the like.

In the compound of Formula IIa, the radical R_{1a} can, if desired, be converted into hydrogen using customary methods for removing the protecting group. However, this conversion is preferably effected after the compound of the Formula IIa has reacted with the compound of the Formula III.

The compounds of the Formula III can be prepared in accordance with customary methods, for example in a manner analogous to that described in WO 97/25324.

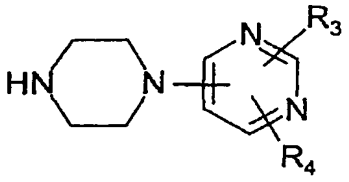
Process B

The compounds according to the invention can also be prepared by reacting a compound of the Formula IV



IV

with a compound of the Formula V



V

in which Y_2 represents a leaving group which can be displaced nucleophilically, for example halogen, in particular chlorine, bromine or iodine, C_1-C_6-alkylsulphonyloxy or C_6-C_{10}-arylsulphonyloxy, and R_1, R_2, R_3, R_4 and n have the meaning which have already been indicated.

The reaction preferably takes place in a diluent and in the presence of a base. Suitable diluents and bases are those mentioned above.

The compounds of the Formula V are known or can be prepared in a customary manner, for example in accordance with methods which are analogous to those described in WO 97/25324. The compounds of the Formula IV can be prepared in a customary manner, for example by reacting a compound of the Formula II with an α,ω-C_2-C_6-alkanediol, and converting the aliphatic OH group in the resulting intermediate into a leaving group which can be displaced nucleophilically.

The pyrimidinoxyalkylpiperazines according to the invention are selective dopamine D_3 receptor ligands which act regioselectively in the limbic system and, because of their low affinity for the D_2 receptor, have

fewer secondary effects than do the classic neuroleptic agents, which are D_2 receptor antagonists. The compounds can therefore be used for treating diseases which respond to dopamine D_3 ligands, i.e. they are effective for treating those diseases in which modulation of the dopamine D_3 receptors leads to an improvement of the disease picture or to the disease being cured. Examples of diseases of this nature are diseases of the central nervous system, in particular schizophrenia, emotional disturbances, neurotic, stress and somatoform disturbances, psychoses, attention deficit disorders, amnestic and cognitive disturbances, such as impaired learning and memory (impaired cognitive function), depression and addiction diseases.

The addiction diseases include the psychic disturbances and behavioural disturbances caused by the abuse of psychotropic substances, such as pharmaceuticals or drugs, and also other addiction diseases, such as compulsive gambling (impulse control disorders not elsewhere classified). Examples of addication-generating substances are: opioids (e.g. morphine, heroin and codeine); cocaine; nicotine; alcohol; substances which interact with the GABA-chloride channel complex, sedatives, hypnotics or tranquilizers, for example benzodiazepines; LSD; cannabinoids; psychomotor stimulants, such as 3,4-methylenedioxy-N-methylamphetamine (ecstasy); amphetamine and amphetamine-like substances, such as methyl phenidate, or other stimulants, including caffeine. Addition-generating substances which particularly come into consideration are opioids, cocaine, amphetamine or amphetamine-like substances, nicotine and alcohol.

The compounds according to the invention are preferably employed for treating emotional disturbances; neurotic, stress and somatoform disturbances and psychoses, schizophrenia, depression or addiction diseases.

For treating the abovementioned diseases, the compounds according to the invention are administered orally or parenterally (subcutaneously, intravenously, intramuscularly or intraperitoneally), in a customary manner. The compounds can also be administered through the nasopharynx using vapours or sprays. However, administration preferably takes place orally.

The dosage depends on the age, condition and weight of the patient and on the mode of administration. As a rule, the daily dose of active compound is from about 10 to 1 000 mg per patient and day when administered orally.

The invention also relates to pharmaceutical compositions which comprise the pyrimidinoxyalkylpiperazines according to the invention and/or their salts. These compositions are present in the customary galenic administration forms in solid or liquid form, for example as tablets, film tablets, capsules, powders, granules, sugar-coated tablets, suppositories, solutions or sprays. In this connection, the active compounds can be processed together with the customary galenic auxiliary substances, such as tablet binders, fillers, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, retardants, antioxidants and/or propellant gases (cf. H. Sucker et al., Pharmazeutische Technologie [Pharmaceutical technology], Thieme-Verlag, Stuttgart, 1978). The resulting administration forms customarily comprise the active compound in a quantity of from 1 to 99% by weight.

The following examples serve to explain the invention without delimiting it.

Examples

Example 1

4-[4-(3-{[4-(Benzyloxy)-2-pyrimidinyl]oxy}propyl)-1-piperazinyl]-2,6-di-tert-butylpyrimidine

Preparing the starting compounds:

A 1) 4-(Benzyloxy)-2-(methylmercapto)pyrimidine

16.4 g (151 mmol) of benzyl alcohol were added dropwise, and under a protective gas, to a suspension of 6.8 g (227 mmol) of sodium hydride (80% strength) in 150 ml of dioxane, and the mixture was stirred at 100°C for 30 min. A solution of 24.3 g (151 mmol) of 4-chloro-2-(methylmercapto)pyrimidine in 100 ml of dioxane was added dropwise, at 50°C, to this suspension, and the mixture was subsequently stirred for a further two hours at 50°C. After the reaction had come to an end, the mixture was acidified with glacial acetic acid, treated with water and extracted several times with dichloromethane. The combined organic phases were dried over sodium sulphate, filtered and evaporated.
Yield: 12.5 g (87% of theory)

^{1}H NMR ($CDCl_3$): δ = 2.5 (s, 3H); 5.5 (s, 2H); 6.4 (d, 1H); 7.4-7.5 (m, 5H); 8.3 (d, 1H).

A 2) 4-(Benzyloxy)-2-(methylsulphonyl)pyrimidine

34.7 g (150 mmol) of A 1) were treated, in a dichloromethane/water two-phase system (volume ratio 4/3) and at from -5° to 0°C, with chlorine gas until the solution was saturated. The mixture was subsequently flushed with nitrogen and heated to room temperature. For the working-up, the phases were separated, the aqueous phase was re-extracted with dichloromethane, and the combined organic phases were dried over sodium sulphate, filtered and evaporated. The residue was purified chromatographically (silica gel, dichloromethane containing 1% methanol).

Yield: 17 g (46% of theory) of a colourless oil

^{1}H NMR ($CDCl_3$): δ = 3.3 (s, 3H); 5.5 (s, 2H); 6.9 (d, 1H); 7.3-7.5 (m, 5H); 8.5 (d, 1H).

B 1) 2,6-di-tert-Butyl-4-pyrimidinol

The above pyrimidine was synthesized, in a manner known per se, by condensing 2,2-dimethylpropionamidine with ethyl trifluoroacetoacetate and sodium methoxide in ethanol, see Heterocyclic Compounds, Vol. 52, The Pyrimidines, p. 189 ff., D.J. Brown et al. (Eds.) John Wiley and Sons, 1994.
m.p. 169°C

B 2) 2,6-di-tert-Butyl-4-chloropyrimidine

Phosphorus oxychloride or thionyl chloride was used, in a manner known per se, to convert the hydroxypyrimidine from step B 1) into the chloro compound, see Heterocyclic Compounds, Vol. 52, The Pyrimidines, p. 329 ff., John Wiley and Sons, 1994.
The compound is present as a yellowish oil.

B 3) 2,6-di-tert-Butyl-4-(1-piperazinyl)pyrimidine

18 g (0.18 mol) of piperazine were dissolved in 25 ml of ethanol. While boiling at reflux, a solution of 7.2 g (0.03 mol) of the chloride obtained in accordance with B 2), dissolved in 10 ml of ethanol, was added dropwise to it within the space of 1 h. After 30 min, the mixture was left to cool. 200 ml of water was then added to the mixture and the whole was extracted with a total of 200 ml of methylene chloride in several portions. The combined organic phase was subsequently washed with water, dried with anhydrous sodium sulphate and concentrated. The desired compound was obtained as a yellowish oil, which was subjected to further processing as the crude compound.

Yield: 98% of theory

B 4) 3-[4-(2,6-di-tert-Butyl-4-pyrimidinyl)-1-piperazinyl]-1-propanol

3.7 g (36 mmol) of triethylamine, 8.33 g (30 mmol) of the compound described under B 3) and 30 mg of sodium iodide were added consecutively to a solution of 5.0 g (36 mmol) of 3-bromo-1-propanol in 40 ml of tetrahydrofuran and the mixture was heated while boiling for 14 h. For the working-up, the salts were filtered off, the mother liquor was concentrated in vacuo, the residue was taken up in dichloromethane and the organic phase was washed twice with water. The combined organic phases were dried over sodium sulphate and filtered, and the filtrate was evaporated. The residue was purified chromatographically (silica gel, dichloromethane/methanol = 97/3).
Yield: 5.4 g (83% of theory)

^{1}H NMR ($CDCl_3$): δ = 1.3 (s, 9H); 1.4 (s, 9H); 1.8 (q, 2H); 2.6 (m, 4H); 2.7 (t, 2H); 3.6 (t, 4H); 3.9 (t, 2H); 6.2 (s, 1H).

Preparing the title compound

2.3 g (6.8 mmol) of the compound prepared under B 4) were dissolved in 25 ml of dimethylformamide and deprotonated with 0.3 g (8.5 mmol) of sodium hydride; a solution of 1.8 g (6.8 mmol) of the compound prepared under A 2) above in 15 ml of DMF was then added and, after 16 h at room temperature, the mixture was hydrolysed with ice water and extracted with methyl tert-butyl ether. The combined organic phases were dried over sodium sulphate and filtered, and the filtrate was evaporated. The residue was purified chromatographically (silica gel, dichloromethane/methanol = 97/3).
Yield: 0.9 g (25% of theory)

^{1}H NMR ($CDCl_3$): δ = 1.3 (s, 9H); 1.4 (s, 9H); 2.1 (m, 2H); 2.5-2.6 (m, 6H); 3.6 (m, 4H); 4.5 (t, 2H); 5.5 (m, 2H); 6.3 (s, 1H); 6.4 (d, 1H); 7.3-7.5 (m, 5H); 8.2 (d, 1H).

Example 2

2-{3-[4-(2,6-di-tert-Butyl-4-pyrimidinyl)-1-piperazinyl]propoxy}-4-pyrimidinol

0.4 g (0.8 mmol) of the compound described in Example 1 was dissolved in 40 ml of ethyl acetate and hydrogenated with hydrogen in the presence of 10 mol% of palladium on charcoal and at atmospheric pressure. After the reaction had come to an end, the catalyst was filtered off and the filtrate was concentrated and the residue was purified chromatographically (silica gel, dichloromethane/methanol = 97/3).
Yield: 0.25 g (76% of theory).

^{1}H NMR ($CDCl_3$): δ = 1.3 (s, 9H); 1.4 (s, 9H); 2.0 (q, 2H); 2.5 (m, 6H); 3.6 (m, 4H); 4.5 (t, 2H); 6.1 (d, 1H); 6.3 (s, 1H); 7.8 (d, 1H).

$C_{23}H_{36}N_6O_4S$ (428.6) m.p.: 149-151°C

The following examples of compounds of the general Formula I were obtained in an analogous manner.

Example 3

4-(Benzyloxy)-2-(4-{4-[2-tert-butyl-6-(trifluoromethyl)-4-pyrimidinyl]-1-piperazinyl}butoxy)-5-methylpyrimidine

m.p. 88-90°C (hydrochloride)

Example 4

4-(Benzyloxy)-2-(3-{4-[2-tert-butyl-6-(trifluoromethyl)-4-pyrimidinyl]-1-piperazinyl}propoxy)-5-methylpyrimidine

m.p. 116-120°C (hydrochloride)

Example 5

2-(3-{4-[2-tert-Butyl-6-(trifluoromethyl)-4-pyrimidinyl]-1-piperazinyl}propoxy)-5-methyl-4-pyrimidinol

m.p. 94-96°C (hydrochloride)

Example 6

4-[4-(3-{[4-(Benzyloxy)-2-pyrimidinyl]oxy}propyl)-1-piperazinyl]-2-tert-butyl-6-(trifluoromethyl)pyrimidine

m.p. 87°C (hydrochloride)

Example 7

2-(4-{4-[2-tert-Butyl-6-(trifluoromethyl)-4-pyrimidinyl]-1-piperazinyl}butoxy)-5-methyl-4-pyrimidinol

^{1}H NMR ($CDCl_3$): δ = 1.4 (s, 9H); 1.6 (m, 2H); 1.8 (m, 2H); 2.0 (s, 3H); 2.5 (t, 2H); 2.6 (m, 4H); 3.7 (m, 4H); 4.4 (t, 2H); 6.6 (s, 1H); 7.6 (s, 1H); 10.4 (br,

OH).

$C_{22}H_{31}F_3N_6O_2$ (468.5) $[M+H^+]$ = 469.3

Example 8

2-(3-{4-[2-tert-Butyl-6-(trifluoromethyl)-4-pyrimidinyl]-1-piperazinyl}propoxy)-4-pyrimidinol

m.p. 164-165°C

Example 9

2-(3-{4-[2-tert-Butyl-6-(trifluoromethyl)-4-pyrimidinyl]-1-piperazinyl}propoxy)-6-methyl-4-pyrimidinol

m.p. 155-156°C

Example 10

2-tert-Butyl-4-(4-{3-[(4-methoxy-2-pyrimidinyl)oxy]-propyl}-1-piperazinyl)-6-(trifluoromethyl)pyrimidine

$C_{21}H_{29}F_3N_6O_2$ (454.5)

Example 11

4-[4-(4-{[4-(Benzyloxy)-2-pyrimidinyl]oxy}butyl)-1-piperazinyl]-2-tert-butyl-6-(trifluoromethyl)-pyrimidine

m.p. 79-80°C (hydrochloride)

Example 12

4-[4-(3-{[4-(Benzyloxy)-2-pyrimidinyl]oxy}propyl)-1-piperazinyl]-2-tert-butyl-6-propylpyrimidine

m.p. 146-148°C (fumarate)

Example 13

2-{3-[4-(2-tert-Butyl-6-propyl-4-pyrimidinyl)-1-piperazinyl]propoxy}-4-pyrimidinol

m.p. 168-169°C (fumarate)

Examples of pharmaceutical administration forms

A) Tablets

Tablets of the following composition are pressed on a tablet press in the customary manner:

40 mg of the substance from Example 2
120 mg of maize starch
13.5 mg of gelatin
45 mg of lactose
2.25 mg of Aerosil® (chemically pure salicic acid in submicroscopically fine dispersion)
6.75 mg of potato starch (as a 6% paste)

B) Sugar-coated tablets

20 mg of the substance from Example 2
60 mg of core substance
70 mg of saccharification substance

The core substance consists of 9 parts of maize starch, 3 parts of lactose and 1 part of vinylpyrrolidine-vinyl acetate copolymer 60:40. The saccharification substance consists of 5 parts of cane sugar, 2 parts of maize starch, 2 parts of calcium carbonate and 1 part of talc. The sugar-coated tablets which are prepared in this way are subsequently provided with a gastric juice-resistant coating.

Biological investigations - receptor binding studies

1) D_3-binding test

Cloned human D_3 receptor-expressing CCL 1,3 mouse fibroblasts, obtainable from Res. Biochemicals Internat. One Strathmore Rd., Natick, MA 01760-2418 USA, were employed for the binding studies.

Cell preparation

The D_3-expressing cells were multiplied in RPMI-1640 containing 10% fetal calf serum (GIBCO No. 041-32400 N); 100 U of penicillin/ml and 0.2% streptomycin (GIBCO BRL, Gaithersburg, MD, USA). After 48 h, the cells were washed with PBS and incubated for 5 min with PBS containing 0.05% trypsin. After that, the cell suspension was neutralized with medium and cells were collected by centrifuging at 300 g. For lysing the cells, the pellet was briefly washed with lysis buffer (5 mM Tris-HCl, pH 7.4, containing 10% glycerol) and, after that, incubated at 4°C for 30 min at a concentration of 10^7 cells/ml of lysis buffer. The cells were centrifuged at 200 g for 10 min and the pellet was stored in liquid nitrogen.

Binding tests

For the D_3-receptor-binding test, the membranes were suspended in incubation buffer (50 mM Tris-HCl, pH 7.4, containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$, 10 mM quinolinol, 0.1% ascorbic acid and 0.1% BSA) at a concentration of approx. 10^6 cells/250 ml of test mixture and incubated with 0.1 nM ^{125}iodine sulpiride at 30°C in the presence and absence of test substance. Nonspecific binding was determined using 10^{-6}M spiperone.

After 60 min, the free radioligand and the bound radioligand were separated by filtration through GF/B

glass fibre filters (Whatman, England) on a Skatron cell collector (Skatron, Lier, Norway), and the filters were washed with ice-cold Tris-HCl buffer, pH 7.4. The radioactivity which had collected on the filters was quantified using a Packard 2200 CA liquid scintillation counter.

The K_i values were determined by means of nonlinear regression analysis using the LIGAND program.

2) D_2-binding test

Cell culture

HEK-293 cells possessing stably expressed human dopamine D_2A receptors were cultured in RPMI 1640 containing Glutamax I™ and 25 mM HEPES containing 10% fetal calf serum. All the media contained 100 units of penicillin per ml and 100 µg of streptomycin/ml. The cells were kept at 37°C in a moist atmosphere containing 5% CO_2.

The cells were prepared for binding studies by trypsinizing (0.05% trypsin solution) for 3-5 minutes at room temperature. After that, the cells were centrifuged at 250 g for 10 minutes and treated at 4°C for 30 minutes with lysis buffer (5 mM Tris-HCl, 10% glycerol, pH 7.4). After centrifuging at 250 g for 10 minutes, the residue was stored at -20°C until used.

Receptor binding tests

"Low affinity state" dopamine D_2 receptor using ^{125}I-spiperone (81 TBq/mmol, DuPont de Nemours, Dreieich)

The assay mixtures (1 ml) consisted of 1×10^5 cells in incubation buffer (50 mM Tris, 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$ and 2 mM $CaCl_2$, pH 7.4 with HCl) and 0.1 nM ^{125}I-spiperone (total binding) or, additionally, 1 µM

haloperidol (nonspecific binding) or test substance.

After having been incubated for 60 minutes at 25°C, the assay mixtures were filtered through GF/B glass fibre filters (Whatman, England) on a Skatron cell collector (from Zinsser, Frankfurt), and the filters were washed with ice-cold 50 mM Tris-HCl buffer, pH 7.4. The radioactivity which had collected on the filters was quantified using a Packard 2200 CA liquid scintillation counter.

The experiment was analysed as above.

The K_i values were determined by nonlinear regression analysis using the LIGAND program or by converting the IC_{50} values using the Cheng and Prusoff Formula.

In these tests, the compounds according to the invention exhibit very good affinities at the D_3 receptor (< 1 μmolar, in particular < 100 nmolar) and bind selectively to the D_3 receptor.

Test for oral bioavailability

The test substances were administered to male Wistar rats in parallel experiments, in one case intravenously (tail vein, 2 mg/kg of body weight) and in the other case orally (by gavage, 10 mg/kg of body weight). For the intravenous administration, the test compound was dissolved in physiological sodium chloride solution containing 1 vol% dimethyl sulphoxide while, for the oral administration, it was dissolved in water containing 0.5% hydroxymethylpropyl cellulose. At different times (intravenously: 0.083; 0.25; 0.5; 2; 8 and 24 h; orally: 0.5; 1; 3; 8 and 24 h) after the administration, two rats were anaesthetized with dinitrogen oxide and a blood sample was withdrawn. Centrifugation was used to obtain plasma samples in which the concentration of the test compound was

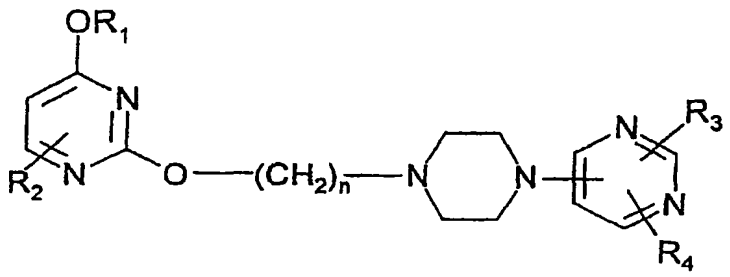
determined using coupled liquid chromatography/mass spectroscopy. The area under the plasma concentration time curve (AUC) was calculated from the results which were obtained using the trapezium method [$((t_n-t_{n-1})\times(c_n+c_{n-1})/2)$, in which t_n is the time of the determination and t_{n-1} is the time of the preceding determination, and c_n and c_{n-1} are the plasma concentrations at times t_n and t_{n-1}, respectively]. The bioavailability was determined in accordance with the Formula

$$\frac{AUC_{oral} \times dose_{intravenous}}{AUC_{intravenous} \times dose_{oral}}.$$

It was found that the compounds according to the invention exhibited a bioavailability which was markedly higher than that of comparison compounds which did not correspond to the Formula I.

Patent Claims

1. Pyrimidinoxyalkylpiperazines of the Formula I:



I

in which:

n represents an integer from 2 to 6,

R_1 represents H, C_1-C_6-alkyl or phenyl-(C_1-C_6)-alkyl in which the phenyl radical can be substituted by one or more substituents selected from C_1-C_6-alkyl and C_1-C_6-alkoxy,

R_2 represents H, C_1-C_4-alkyl, OH, C_1-C_6-alkoxy, NH_2 or C_1-C_6-halogenoalkyl,

R_3 and R_4, independently of each other, represent H, C_1-C_6-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-halogenoalkyl, pyrrolyl or phenyl, which latter can be substituted by one or more substituents selected from C_1-C_6-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxy, OH, halogen or C_1-C_6-halogenoalkyl, phenyl, cyano or nitro,

with the proviso that the radicals R_3 and R_4 on the pyrimidine ring are in each case arranged in the m position in relation to each other and to the piperazine substituent on the pyrimidine ring, and at least one of the radicals R_3 and R_4 represents C_3-C_6-alkyl or C_3-C_6-hydroxyalkyl, which in each case possesses a branched alkyl chain or is bonded

to the pyrimidine ring by way of a secondary carbon atom, or trifluoromethyl,

and their piperazine-N-oxides and salts with pharmaceutically tolerated acids.

2. Pyrimidinoxyalkylpiperazines of the Formula I according to Claim 1, in which at least one of the radicals R_3 and R_4 represents C_3-C_6-alkyl or C_3-C_6-hydroxyalkyl which in each case is bonded to the pyrimidine ring by way of a secondary or tertiary carbon atom.

3. Pyrimidinoxyalkylpiperazines of the Formula I according to Claim 1 or 2, in which R_1 represents H or benzyl whose phenyl radical can be substituted by one or more C_1-C_6-alkoxy radicals.

4. Pyrimidinoxyalkylpiperazines of the Formula I according to Claim 3, in which R_1 represents H.

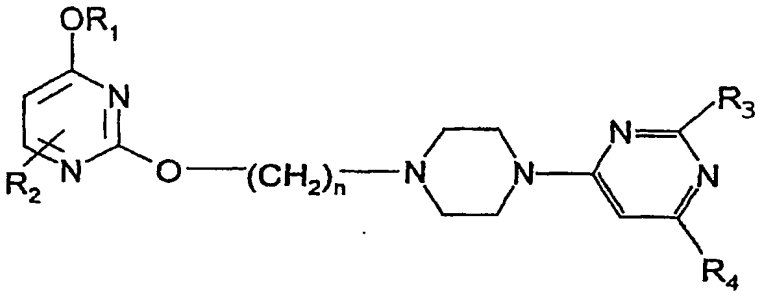
5. Pyrimidinoxyalkylpiperazines of the Formula I according to one of the preceding claims, in which R_2 represents H, methyl, ethyl, OH, C_1-C_6-alkoxy, trifluoromethyl or difluoromethyl.

6. Pyrimidinoxyalkylpiperazines of the Formula I according to Claim 5, in which R_2 represents H or OH.

7. Pyrimidinoxyalkylpiperazines of the Formula I according to one of the preceding claims, in which R_3 and R_4, independently of each other, represent H, C_1-C_6-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-halogenoalkyl or phenyl, which latter can be substituted by one or more substituents selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen or phenyl.

8. Pyrimidinoxyalkylpiperazines of the Formula I according to one of the preceding claims, in which n represents 3 or 4.

9. Pyrimidinoxyalkylpiperazines according to Claim 1 of the Formula Ia



Ia

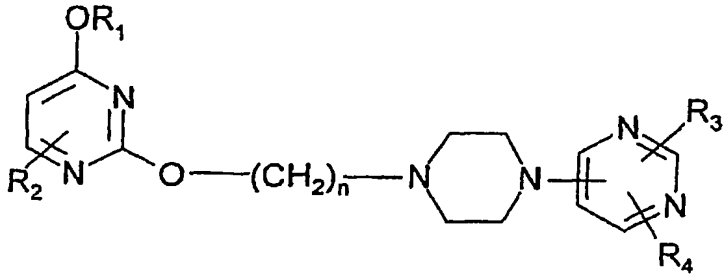
in which R_1, R_2, R_3, R_4 and n have the meaning given in Claim 1.

10. Pyrimidinoxyalkylpiperazines of the Formula Ia according to Claim 9, in which R_3 represents C_3-C_6-alkyl which is bonded to the pyrimidine ring by way of a tertiary carbon atom, and

R_4 represents C_1-C_6-alkyl, C_1-C_6-halogenoalkyl or phenyl, which latter can be substituted by one or more substituents selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen or phenyl.

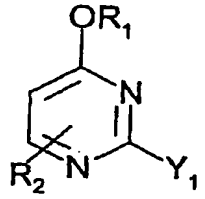
11. Pyrimidinoxyalkylpiperazines of the Formula Ia according to Claim 9, in which R_3 represents trifluoromethyl, and R_4 represents C_1-C_6-alkyl, C_1-C_6-halogenoalkyl or phenyl.

12. Process for preparing a pyrimidinoxyalkylpiperazine of the Formula I



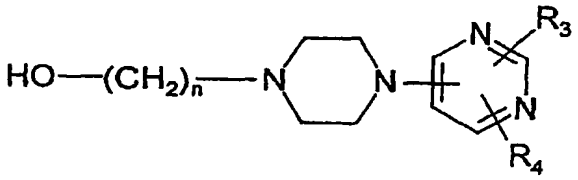
I

in which a compound of the Formula II



II

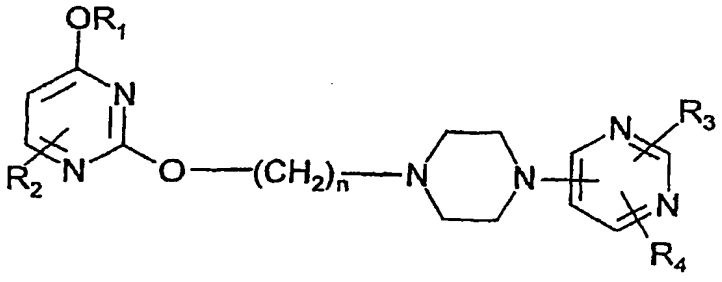
is reacted with a compound of the Formula III



III

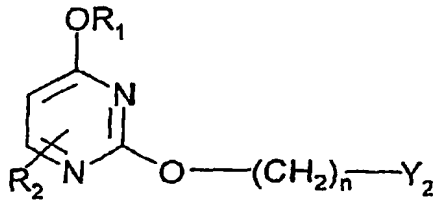
in which Y_1 represents a leaving group which can be displaced nucleophilically and R_1, R_2, R_3, R_4 and n have the meaning given in Claim 1.

13. Process for preparing a pyrimidinoxyalkylpiperazine of the Formula I



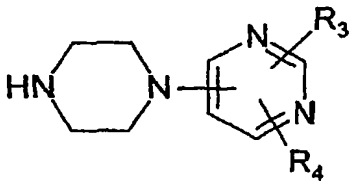
I

in which a compound of the Formula IV



IV

is reacted with a compound of the Formula V



V

in which Y_2 represents a leaving group which can be displaced nucleophilically and R_1, R_2, R_3, R_4 and n have the meaning given in Claim 1.

14. Pharmaceutical composition, which comprises at least one compound according to one of Claims 1 to 11, where appropriate together with physiologically acceptable excipients and/or adjuvants.

15. Use of at least one compound according to one of Claims 1 to 11 for producing a pharmaceutical composition for treating diseases which respond to modulation of the dopamine D_3 receptor.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/07183

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/34 A61K31/505 A61P25/18 A61P25/24 A61P25/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2000 067847 A (BASF A.-G., GERMANY) 16 November 2000 (2000-11-16) page 1, line 7 - line 10; examples 10,11,19 page 3, line 1 -page 6, line 21 page 11, line 28 -page 12, line 7 ---	1-11,14, 15
Y	WO 97 25324 A (BASF AG ;UNGER LILIANE (DE); WICKE KARSTEN (DE); BLANK STEFAN (DE)) 17 July 1997 (1997-07-17) cited in the application page 5, line 11 - line 19; claims 1,15,16; examples 34,1-3,31,21,488,492,500,505,512,528,535,542,546 examples 549,561,559,564,569,570 --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2002	09/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hanisch, I

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/07183

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 02519 A (BASF AG ;HELLENDAHL BEATE (DE); LANSKY ANNEGRET (DE); MUNSCHAUER R) 1 February 1996 (1996-02-01) cited in the application page 5, line 1 - line 12; claims 1,13,15,16; example 48; table 7	1-15

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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Information on patent family members

International A ation No
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